Exhibit 101

Asbestos and ovarian cancer: examining the historical evidence

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ABSTRACT

Asbestos recently returned to the spotlight when Johnson & Johnson halted sales of baby powder due to lawsuits claiming that the talc in baby powder may have been contaminated with asbestos, which has been linked to the risk of ovarian cancer development. Although talc and asbestos have some structural similarities, only asbestos is considered causally associated with ovarian cancer by the WHO's International Agency for Research on Cancer. While it is useful to understand the types and properties of asbestos and its oncologic biology, the history of its association with ovarian cancer is largely based on retrospective observational studies in women working in high asbestos exposure environments. In reviewing the literature, it is critical to understand the distinction between associative risk and causality, and to examine the strength of association in the context of how the diagnosis of ovarian cancer is made and how the disease should be distinguished from a similar appearing but unrelated neoplasm, malignant mesothelioma. Based on contextual misinterpretation of these factors, it is imperative to question the International Agency for Research on Cancer's assertion that asbestos has a clear causal inference to ovarian cancer. This has important clinical implications in the way patients are conceivably counseled and provides motivation to continue research to improve the understanding of the association between asbestos and ovarian cancer.

INTRODUCTION

Asbestos may be responsible for up to 255 000 deaths per year[1] worldwide and recently returned to the spotlight as Johnson & Johnson withdrew all sales of baby powder from North American markets due to thousands of lawsuits by women with ovarian cancer who claimed that their cancers were caused by asbestos.[2–4] Underpinning these claims is the assertion that talc in baby powder may have contained asbestos.[5] Asbestos has been linked to ovarian cancer since the middle of the 20th century when physicians in England first suspected an increased incidence in women exposed to asbestos in working conditions.[6] By this point, doctors were already sounding the alarm about the pulmonary toxicity and the role of asbestos in a previously rarely described cancer, malignant mesothelioma.[7] Furthermore, there seemed to be an obvious connection between malignant mesothelioma arising in the background of lung asbestosis in these workers. There was no discernible antecedent condition or lesion definitively coupling asbestos to ovarian cancer, even in these women highly exposed to asbestos at work.

Additional studies described a potential link to ovarian cancer in women directly working with asbestos and its products but also in women with occult asbestos exposure through their reproductive,[8] digestive,[9] or respiratory[10] tracts. It has been hypothesized that women with no personal exposure could still have ovaries exposed to asbestos through sexual intercourse or household cleaning when the women's partners were exposed to asbestos, but this was not linked to ovarian cancer.[8 11 12] Talc further became 'guilty by association' for its implication as a vehicle for occult asbestos exposure.[13] Not only was talc minerally similar to asbestos (and studied for its potential carcinogenic effect),[14 15] but more importantly, talc also purportedly harbored asbestos as a result of mining talc rock deposits that contained asbestos.[13 16] Many observational studies associated cosmetic talc applied perineally and ovarian cancer.[17 18] More recently, however, a larger prospective observational study failed to find an increase in ovarian cancer in women who used perineal talc.[19] Talc has been included in many products other than baby powder, including birth control pills, condoms, female diaphragms, and crayons.[13] The WHO's International Agency on Cancer Research (IARC) produced monographs that reviewed the evidence associating both asbestos and talc with ovarian cancer. In the monograph assessing the link between ovarian cancer and talc, only limited evidence of a connection was described.[14]

Asbestos is the hypothetical link between talc and ovarian cancer, independent of talc and any direct effect it might have.[10 17] The IARC initially cited asbestos as a carcinogen to humans in 1973.[20] Since 2009, the IARC found asbestos to have a 'clearly established' causal association with ovarian cancer, based primarily on five cohort studies.[21 22] This presents the opportunity for clinicians and researchers involved in the study of ovarian cancer to review asbestos, its history, and its hypothesized pathogenesis in malignant mesothelioma and ovarian cancer and their diagnostic similarities, and therefore to understand the evidence for association or causation, specifically the material focused on by the IARC.

What is Asbestos?

Asbestos is the name given to a family of small silicate fibers found and mined in nature since ancient

Greece.[23 24] The fibers could be woven into materials or admixed with other industrial products to improve thermal resistance. The various fibers are grouped into two families: serpentine and amphibole. Serpentine fibers include mineral chrysotile, commonly referred to as white asbestos, which accounts for 90% of the world's production of asbestos.[25] The amphibole family of minerals includes amosite (brown asbestos), crocidolite (blue asbestos), and less common fibers of anthophyllite, actinolite, and tremolite. Among both serpentine and amphibole asbestos, crocidolite is generally accepted as the most carcinogenic. Despite its abundance, there remains controversy as to whether chrysolite is itself pathogenic or whether its contamination with amphibole fibers is the primary cause of cancer.[26 27]

What is the Evidence that Asbestos Causes Cancer?

Connecting asbestos (the cause) and ovarian cancer (the effect) is challenging as there are no randomized experimental trials. Almost any trial designed would likely be challenging due to its necessary scope and unethical nature, given the exposure to a human carcinogen. Even retrospective trials can be limited by feasibility.[28] As a result of these limitations, epidemiologic studies are employed but cannot replace the direct and measured intervention in a controlled experiment. In order to compensate for this, assessing causal from non-causal associations requires an observer to assess the strength and consistency of the association.[18] Additional factors considered include—but are not limited to—temporality (cause preceding effect), gradient response (dose-dependent effect), and the existence/presence of a plausible biological rationale for the association.

For example, there is a strongly plausible biological mechanism and dose dependency for the development of pleural and peritoneal malignant mesothelioma after asbestos administration in *in vivo* models.[29 30] Although there is no question that asbestos causes certain cancers, the exact manner in which it is carcinogenic has not been fully elucidated.[25] There are several hypotheses, including one that claims there are transition metals embedded in asbestos fibers that create reactive oxygen species.[31] This oxidative stress causes—possibly through 'frustrated phagocytosis of macrophages'—changes to nearby mesothelial cells.[32] Directly on mesothelial cells, *in vitro* exposure of asbestos is highly cytotoxic but some cells may evade immediate cell death by activation of the AP-1 pathway, mediating expression of tumor necrosis factor-α receptors that prevent cell death through nuclear factor-B activation.[33] In this case, asbestos is hypothesized to be protective against apoptosis. Other ways in which asbestos has been found possibly to be linked to cancer are the *in vitro* changes leading to expression of interleukin 13, basic fibroblast growth factor, granulocyte colony-stimulating factor, and vascular endothelial growth factor protein levels on mesothelial cell lines.[31] Other studies, however, have found chromosomal alterations as a prominent factor in asbestos-related cellular changes.[34] An additional branch of research has focused on Simian virus 40 as a possible co-carcinogen along with asbestos.[35 36] More recently, evidence has emerged for BAP1 and the Hippo pathway activation as potentially targetable in pleural malignant mesothelioma.[37–39]

The mechanisms by which asbestos causes ovarian-specific tumorigenesis also require further explanation. Early studies noted cell death but could not generate *in vitro* findings consistent with the development of cancer.[40 41] Furthermore, different asbestos fibers were used and caused different levels of cytotoxicity in animal ovarian cells.[40–43] In more recent studies of human ovarian epithelial cell lines, modulated expression of ATF3 was found.[44] Similar to *in vitro* studies of mesothelial cell lines,[31] this leads to increased production of inflammatory cytokines such as interleukin 13 and granulocyte colony-stimulating factor.[44] Experimental research supports possible activation of pro-inflammatory and anti-apoptotic pathways in both malignant mesothelioma and ovarian cancer, but the precise pathogenesis and early molecular triggers remain incompletely understood, are an avenue for future research, and have not necessarily been reviewed by the IARC.

One experiment the IARC specifically highlighted was an *in vivo* study that provided a "biologic plausibility of an association between asbestos exposure and ovarian cancer".[21 45] In that study, tremolite asbestos was injected intra-peritoneally into four mammal species: mice, hamsters, guinea pigs and rabbits. The authors found that only rabbits and guinea pigs produced epithelial changes in the ovaries "similar to the lesions seen in the early ovarian lesions in humans".[45] This may have been due to the fact that several decades later it was found that, in guinea pigs and rabbits, constant estrogen exposure stimulates the "formation of a papillary ovarian surface resembling human serous neoplasms of low malignant potential"'.[46]

HISTORY OF ASBESTOS IN CANCER

In the first half of the 20th century and the increased mechanization brought about in the World Wars, asbestos became widely blended into compounds for its natural ability to insulate from heat and flames. By the 1960s and 1970s, asbestos could be found in everything from insulation to talcum powder.[16] Soon afterwards, English doctors noted an increase in pulmonary morbidity and tumor formation in workers involved in the production of asbestos.[7 47] In 1960, Keal,[6] a physician working in London, first linked ovarian cancer and abdominal neoplasms to patients exposed to asbestos in their working conditions. In a series of 23 women with asbestosis, nine were determined to have died of intra-abdominal malignancy. One "had an ovarian carcinoma, four had peritoneal growths possibly of ovarian origin, and in the remaining four the diagnosis was carcinomatosis peritonei."[6] Subsequent medical research began to explore the association between asbestos and ovarian cancer, especially as mounting evidence showed an increasingly convincing relationship between asbestos and pleural malignant mesothelioma, laryngeal, and lung cancer.[48]

An important consideration for this research became the correct diagnosis and distinction of ovarian cancer from malignant mesothelioma. At the same time that Keal was describing his cohort of patients, two researchers, Enticknap and Smither, reported a surge in both men and women with peritoneal malignant mesothelioma, previously a rare cancer.[49] In this case series, all eight men were described as having peritoneal malignant mesothelioma. Three women reported similar exposures, but two were assumed to have ovarian cancer and one malignant mesothelioma. The authors further argued to recognize peritoneal malignant mesothelioma as a distinct disease and questioned whether Keal, in his earlier paper, could have misdiagnosed malignant mesothelioma as ovarian cancer. If malignant mesothelioma of the peritoneum could

have been misclassified as ovarian cancer, this could introduce bias. Another early and larger study, also from England, surveying a larger population of men and women, evaluated the tumors and found increased rates of malignant mesothelioma in both sexes.[50] Rates of ovarian cancer were not increased for all women, but the study reported a dose-related increase in ovarian cancer in the subset with the highest occupational exposure.

Can Ovarian Cancer be Confused with Malignant Mesothelioma of the Peritoneum?

The ability to differentiate malignant mesothelioma from other cancers in the peritoneum has changed significantly over time with improved pathological techniques and, until 1999, there was no International Classification of Diseases (ICD) code for mesothelioma.[51] This makes many retrospective registry studies that identify deaths from ICD codes difficult to interpret.

The first published studies[6 49] of cancers in the peritoneum described these cancers solely by their histological features but acknowledged the difficulty of distinguishing peritoneal malignant mesothelioma from ovarian cancer by this method alone.[45 50] In general, research has found varying rates of malignant mesothelioma caused by asbestos exposure, depending on the type of asbestos and other possible co-factors such as genetics.[52] Subsequently, attempts were made to quantify the asbestos fiber burden in ovarian tumors and normal ovaries, with and without exposure to asbestos.[8 11 53] Due to the uneven data regarding the asbestos fiber burden in exposed and unexposed women and the technical challenges of measuring fibers in tissue, the IARC did not recommend in its monograph the measurement of fibers to diagnose asbestos-related ovarian cancer.[21] Instead, the IARC recommended the use of immunohistochemistry to clinically separate ovarian cancer from malignant mesothelioma.

It was not until the 1970s that immunohistochemistry became more widely available and used.[54–56] About 20% of malignant mesothelioma arise from the peritoneum,[57 58] but there is still a high rate of misdiagnosis.[59–62] Improved techniques and immunostains such as Paired Box Gene 8 (PAX-8) to determine the Müllerian origin of a tumor have significantly improved the ablity of pathologists to differentiate ovarian cancer from malignant mesothelioma (Table 1).[60 63–65] Despite the adoption of PAX-8 immunostaining over roughly the last decade, the diagnosis is still challenging.[66] As awareness of peritoneal malignant mesothelioma has become more prevalent, recent population studies with better pathology registry data have shown starkly increased mortality/incidence ratio for peritoneal malignant mesothelioma in women compared with men.[67]

Compounding the difficulty of histologic diagnosis are the obstacles associated with obtaining pathologic specimens to review from observational and retrospective studies. This complication is illustrated in a pair of recent Italian studies that assessed the rates of cancer from death certificates and medical records in a population of Italian women exposed to asbestos.[68 69] In their initial research,[68] the authors found an increased standardized mortality ratio (SMR) of 3.03 (95% CI 1.69 to 4.99) for ovarian cancer in women exposed to textile work in Northern Italy. A subsequent study by the same group sought to validate immunohistochemical BAP1 expression in malignant mesothelioma from the same group of women and additional men exposed, for a total number of 1977 patients.[69] In an attempt to identify only malignant mesothelioma pathology samples from this population, they found 127 patients with asbestos-related cancers by death certificates, but only had medical records for 57% of them. A further 7% of these cases were not malignant mesothelioma when the medical records or pathology were reviewed during central pathology review. The authors could only confirm 27.5% of the original 127 patients as true cases of malignant mesothelioma on pathology review. This represents less than 2% of the total number of patients in the cohort they identified with exposure to asbestos. The limited ability to confirm cancer pathology for the majority of the patients in this study confirms the importance of the question whether misdiagnosis of ovarian cancer can bias epidemiologic data regarding asbestos exposure.

OBSERVATIONAL EVIDENCE OF ASBESTOS CAUSING OVARIAN CANCER

What is the Primary Evidence the IARC used to Conclude that Ovarian Cancer was Caused by Asbestos?

The IARC Working Group reviewed more than 12 studies in order to assess the role of asbestos in ovarian cancer.[21] The Group's opinion that asbestos caused ovarian cancer "was clearly established on

Table 1 Immunohistochemical differentiation between ovarian cancer and peritoneal malignant mesothelioma

Marker	pMM	OC	References and comments
Wilms' tumor 1 antigen (WT1)	++	++	Limited use due to poor specificity in determining mesothelial origin[83–86]
Calretinin	++	+	Insufficiently specific[65 84–86]
Cytokeratin 5/6	+	+	Limited use; can be focal, patchy, or weak[83–85]
Mesothelin	+	+	Insufficiently specific[65 84]
D2-40	++	+	D2-40 will stain epithelioid vascular tumors; it is not a good marker for this differential diagnosis[65 83]
h-caldesmon	+/–	–	Smooth muscle marker with conflicting studies supporting its use[65 83 87]
MOC-31/BerEP4	–	+	May be focally positive in MPM[84 85]
ER/PR	–	++	MPM can have low positive staining (up to 10%)[65 88]
PAX8	–	++	Some ovarian cancers can have weak staining and weak staining can be seen in a small number of MPM[65 66 83]

MPM, malignant pleural mesothelioma; OC, ovarian cancer; pMM, peritoneal malignant mesothelioma.

Table 2 Studies noted by the International Agency for Research of Cancer 2012 Working Group as primarily establishing a causal connection between asbestos occupational exposure and ovarian cancer[21]

Study	Year	Study summary	Pathology reviewed	Comment
Acheson et al[70]	1982	Cohort study, two groups, 757 women exposed to crocodolite fibers (SMR 2.75, 95% CI 1.42 to 4.81) and 570 exposed to chrysotile (SMR 1.48, 95% CI 0.48 to 3.44)	None	None
Wignall and Fox[71]	1982	Cohort study, 500 women with crocodolite exposure (SMR 2.13, p<0.01)	3/500 samples reviewed. 1/3 ovarian cancer (33%) misdiagnosed, 1 was malignant mesothelioma	Unknown preparation and whether immunostains used prior to 1982 publication date. PAX-8 immunostaining not available at time of publication
Berry et al[75]	2000	Cohort study, 700 women exposed to multiple fiber types (SMR 2.53, 95% CI 1.16 to 4.80)	6/700 samples reviewed. 2/6 ovarian cancer (33%) misdiagnosed, unknown other pathology	Pathology reviewed in prior papers, either in 1969[76] or 1985,[77] unknown stains used prior to 1969 or 1985. PAX-8 immunostaining not available at time of publication
Germani et al[72]	1999	Cohort study, 631 women from registry of women exposed to any fiber type of asbestos (SMR 4.77, 95% CI 2.1 to 9.06)	None	None
Magnani et al[73]	2008	Cohort study, 777 women exposed to mixed fibers (SMR 2.27, p<0.05)	9/777 samples reviewed, 2/9 ovarian cancer cases misdiagnosed (22%), unknown other pathology	Unknown if this was pathologic review or by report. Unknown year or immunostains. PAX-8 immunostaining likely not available at time of publication

SMR, standardized mortality ratio.

five strongly positive cohort mortality studies with heavy occupational exposure to asbestos" (Table 2). The first study by Acheson et al[70] examined two groups of women from separate regions who were exposed to different types of asbestos within wartime gas mask factories. One group of women used crocidolite asbestos and the other group used chrysotile fibers. Of the two groups, only the group of women using crocidolite had an increased SMR of ovarian cancer. The authors acknowledge the "difficulties of the differential diagnosis" between malignant mesothelioma and ovarian cancer, especially as malignant mesothelioma was relatively rarer and the diagnoses came long after exposures.[70] Yet the pathology was not reviewed and the authors maintain that ovarian cancer may be associated with asbestos without any further corroboration. Furthermore, the exposures could have occurred as early as 24 years prior to the time mortality was recorded in 1951. This misses potential confounders in the intervening years, given such a long retrospective window. Furthermore, the historic controls used to compare against the exposed group included mortality data starting in 1968, after theoretic peak wartime exposures.

The second study also reviewed observed versus expected rates of cancers in 500 women who assembled gas masks in World War II.[71] The authors found the number of women with ovarian cancer to be higher in the group of workers exposed compared with expected controls. These authors also acknowledged the risk of misdiagnosis by pathology, but only attempted histologic review of three out of 500 cases. One of the three samples was found to be primary peritoneal malignant mesothelioma. The authors maintained their conclusion that the observed number of ovarian cancers was increased despite a 33% misdiagnosis rate in the less than 1% of reviewed samples. In such a small sample size, additional histology may be critical to establish a strong association between asbestos and ovarian cancer in this population of exposed women.

Two additional studies referenced by the IARC came from Italian cohorts of women with similar occupational exposure to asbestos (Germani et al[72] and Magnani et al[73]). Germani et al[72] retrospectively sifted through a database of women in Italy who had already been compensated for asbestosis and found, compared with national rates, an increased rate of ovarian cancer by mortality report. In addition to the fact that the pathology was not reviewed, there might have been selection bias as these 627 women were already being compensated for asbestos-related lung injury. The second study by Magnani et al[73] found 777 women who had worked in a cement factory with high levels of asbestos. There was a slightly elevated SMR for ovarian cancer (2.27, 95% CI 1.04 to 4.32) in this group of women. Interestingly, however, both of the Italian studies show an unexpected increase in uterine cancers and decrease in laryngeal cancers compared with expected controls.[72 73] Coincidentally, the IARC monograph and the Institute of Medicine's 2006 report on asbestos-related disease both find a clear 'causal association' between asbestos and laryngeal cancer (more than ovarian cancer), yet neither finds an association with uterine cancer.[21 74] While the paper by Magnani et al[73] states in the discussion section that ovarian cancer pathology was confirmed in seven of nine cases, it is unclear how and by whom it was confirmed. The authors do not claim to have reviewed

the pathology independently themselves, so it may be possible that confirmation consisted of a review of the post-mortem examination by non-specialized pathologists. Problematically, as one author concludes, "in Italy in particular … the accuracy of death certification of peritoneal mesothelioma is quite poor, the risk of misclassification with other abdominal neoplasms is relevant, and increased SMRs for these cancer sites should be regarded with caution".[72]

In the study by Berry et al,[75] the fifth referenced directly by the IARC, researchers studied 700 English women who were involved years before in the manufacture of gas masks. They analyzed causes of mortality identified by ICD (International Statistical Classification of Diseases and Related Health Problems) codes and attempted to review the pathology. Of note, there was no ICD code for mesothelioma at the time of the death of these patients.[51] The calculated observed/expected rate for ovarian cancer was 2.53 (95% CI 1.16 to 4.80). This result is undeniably strengthened by the fact that this population was followed for a longer period of time. Potential sources of bias included the retrospective identification of patients by ICD code and the robustness of the pathologic review. The authors described their methods and results of pathologic confirmation in prior studies 15 and 31 years before.[76 77] The first attempt in 1969 only included men, eliminating the possibility of ovarian cancer diagnosis, and found that 15 of the 84 samples (18%) that could be histologically reviewed likely had been deaths due to malignant mesothelioma that were misclassified as other abdominal/peritoneal cancer.[76] The paper claimed that "the pathologic appearances were frequently confused with generalized carcinomatosis of the peritoneum". The second study, in 1985,[77] retrospectively identified 11 ovarian cancers but only had pathologic specimens for six patients. Of these six, two (33%) were censored after being found not to be of ovarian origin and were not included in the analysis to calculate the above observed/expected rate of 2.53. If this percent (33%) of misdiagnosed ovarian cancer was consistent in the samples that could not be reviewed, this might have significantly changed the observed rate of ovarian cancer in this population.

Interestingly, the IARC's Working Group reviewed several papers that showed a non-significant risk of ovarian cancer due to asbestos exposure, but these were not included in the consensus opinion. A census cohort study of a well-maintained national registry from Finland with more than 5000 women which investigated causes of ovarian cancer failed to uncover an association with asbestos.[78] Notably, in this study even women exposed to the highest amounts of asbestos did not have a significantly increased risk of ovarian cancer. An additional case–control study from Norway of women working in high asbestos-exposure printing jobs also failed to find a statistical connection to ovarian cancer.[53] While the Finnish study did not assess pathology, the Norwegian study "used an experienced gynecological oncologist to review all" the pathology.[53]

A recent meta-analysis by Reid et al[79] was also cited in the IARC monograph but not used in forming the Group's opinion. The analysis performed two reviews. First, it reviewed all available studies linking asbestos and ovarian cancer to obtain an increased SMR of 1.75 (95% CI 1.45 to 2.10) compared with reference populations. In the second meta-analysis, the data were re-analyzed for studies that accounted for pathology and there was a non-significant elevation in excess SMR of 1.29 (95% CI 0.97 to 1.7) suspected to be from asbestos. Given the discrepancy, this meta-analysis further confirms the need to have pathologic review particularly since, as the incidence of ovarian cancer in these observational studies is low, the misclassification of a single cancer death may exert an outsize impact on the observed versus expected ratio.

A more recent study by Luberto et al[80] not reviewed by the IARC but with overlapping patient cohorts with the meta-analysis by Reid et al[79] assessed workers in 21 asbestos cement factories in Italy until the ban of asbestos in 1992 (including the aforementioned study by Magnani et al[73] cited by the IARC). The study attempted to assess if there was dose-dependent mortality due to ovarian cancer and stratified deaths from ovarian cancer by years of exposure and date of first exposure.[80] There was a statistically non-significant increase in SMR except for the group of women with the highest exposure whose SMR was 4.38 (95% CI 1.19 to 11.21). Interestingly, although the women exposed for the longest had more time to develop cancers than those exposed later on, the women exposed after 1990 had an SMR of 1034.3 (95% CI 25.9 to 5763.3)—the highest of any study—compared with the non-significant SMRs for all women exposed from 1950 to 1990 (SMR range 1.04–1.32). Furthermore, the study could not corroborate any pathology but assumed a low level of misclassification of malignant mesothelioma (13–25%)[80] from a literature review of studies that included neither women nor ovarian cancer.[51 81 82] The incongruent length of exposure and initiation of exposure, as well as the poor absence of reliable estimation of misclassified pathology in these cohorts, make it difficult to interpret the strength of association in the study by Luberto et al.[80]

SUMMARY

The Working Group carefully considered the possibility that cases of peritoneal mesothelioma may have been misdiagnosed as ovarian cancer, and that these contributed to observed excesses. Contravening that possibility is the finding that three of the studies cited here specifically examined the possibility that there were misdiagnosed cases of peritoneal mesothelioma, and all failed to find sufficient numbers of misclassified cases. The Working Group noted that the possibility of misclassification had probably diminished in recent years because of the development of new immunohistochemical techniques.[21]

The fact that asbestos causes certain cancers is undisputed, even if the pathogenesis requires further elucidation. Some of the clearest evidence of increased risk due to asbestos exposure has been in organs with direct exposure to asbestos dust, such as pleural malignant mesothelioma and laryngeal cancer. Experimentally, there have not been reliable biological explanations *in vitro* or *in vivo* to explain the development of ovarian cancer due to asbestos. Many of the epidemiologic studies of asbestos exposure suffer from additional and shared confounders—namely, the inability to review pathology and to distinguish between ovarian cancer and metastatic (pleural or peritoneal) malignant mesothelioma. From three studies that used pathologic review of specimens there were 1977 patients available and 18 samples reviewed.[71 73 75] Five of the samples (28%) were misdiagnosed, a high rate of misclassification.

Furthermore, based on publication dates and reviewing the methods of these publications, none of the studies on which the IARC based its judgment likely used "new immunohistochemical techniques", as stated by the IARC. None of the studies detailed methods for histology review. The true incidence and mortality of ovarian cancer in women

with occupational exposure to asbestos is obscured by these factors and could significantly bias the interpretation of the studies individually or as a group.

Given the quality of the evidence, the counterargument could be made—namely, that the incidence of the rates of ovarian cancer is actually much higher, and that the peritoneal malignant mesothelioma cases are actually misdiagnosed ovarian cancers. Regardless of this, definitive associations in either direction are difficult to make pertaining to the carcinogenic potential of asbestos in the ovaries from these retrospective cohort studies. Without an expert pathologic review, it is extremely difficult to establish—as the IARC Working Group has intimated—a clear 'causal association' between ovarian cancer and heavy occupational exposure to asbestos.[21]

While there is an observed statistical association between asbestos and ovarian cancer, it is weak and inconsistent. Further scientific investigation is needed to clarify the causal association of asbestos and ovarian cancer. Physicians need to discuss with patients the causal explanation of environmental carcinogens like asbestos. The strength of the association of asbestos with ovarian cancer has important legal ramifications, as evidenced by the fact that asbestos is the putative culprit in talc linked to ovarian cancer. Further research and improved study design are necessary to better establish the strength of these associations.

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